Randomized Trial

Efficacy of Atlantoaxial Joint Glucocorticoid Injection in Patients with Rheumatoid Arthritis: A Randomized Trial

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Background: The atlantoaxial joint (AAJ) plays a pivotal role in the cervical spine motion. Unfortunately, it is the most common cervical spine joint that is affected in patients with rheumatoid arthritis. Inflammation of the AAJ results in neck disability, nerve root compression, and finally spinal cord compression.

Objectives: We aim to evaluate the efficacy of intraarticular triamcinolone injection of the AAJ on neck pain and disability.

Study Design: A prospective randomized, controlled clinical trial.

Setting: An interventional pain unit in a tertiary center at a university hospital in Egypt.

Methods: Sixty patients with rheumatoid arthritis complaining of AAJ arthritis were randomized into 2 groups. Group AAJI (n = 30) received AAJ injection with 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of 20 mg of triamcinolone, in addition to oral placebo tablets (2 tablets every 8 hours for one week). Group SS (n = 30) received systemic steroids, oral prednisolone tablets (5 mg, 2 tablets every 8 hours for one week), in addition to AAJ injection with 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of normal saline solution. The percentage of patients who showed ≥ 50% reduction of their visual analog scale (VAS) pain score (measured at 1, 2, and 3 months postoperatively), VAS pain score and neck disability index (NDI) (measured at 2, 4, 6, 8, and 12 weeks postoperatively), and the magnetic resonance imaging (MRI) changes of AAJ (assessed 4 weeks postoperatively) were all evaluated.

Results: There was significant reduction in the percentage of patients who showed ≥ 50% reduction of their VAS pain score postoperatively in group AAJI compared with group SS at one month (75% vs. 46.45%; $P = 0.033$), 2 months (60.7% vs. 25%; $P = 0.009$), and 3 months (53.6% vs. 17.9%; $P = 0.007$). There was significant reduction in overall VAS and overall NDI in group AAJI compared with group SS (mean ± standard error) (41.5 ± 2.6 vs. 52.1 ± 2.6; $P = 0.005$) and (43.7 ± 3.1 vs. 52.4 ± 3.1; $P = 0.040$), respectively. Analysis of postoperative MRI findings revealed significant improvement of bone marrow edema in group AAJI (AAJI vs. SS) (71.4% vs. 42.9%; $P = 0.033$), also the synovial enhancement disappeared significantly in group AAJI compared with group SS, (16/22 [72.7%] vs. 10/23 [43.5%]; $P = 0.026$), moreover, there was a significant reduction in pannus size in group AAJI compared with group SS, (6/10 [60%] vs. 1/9 [11%]; $P = 0.041$).

Limitations: The study follow-up period was limited to only 3 months.

Conclusions: For acutely inflamed AAJ due to rheumatoid arthritis, AAJ steroid injection is a potential therapeutic option; it decreased cervical neck pain, improved neck mobility, and hastened recovery of the joint from an acute inflammatory stage.

Key words: Rheumatoid arthritis, atlantoaxial joint injection

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Rheumatoid arthritis is an autoimmune disease that predominantly affects adult women (1) and the estimated prevalence is 1%-2% of adult populations worldwide (2).

The cervical spine is affected in up to 85% in patients suffering from rheumatoid arthritis (3). Affect to the cervical spine occurs due to chronic synovitis that results in progressing bone erosion, ligamentous injury, and ultimately disability and loss of function. Unfortunately, the atlantoaxial joint (AAJ) is the most common cervical spine joint that is affected in patients with rheumatoid arthritis (3). Inflammation of the AAJ results in neck disability, nerve root compression, and finally spinal cord compression (4).

Magnetic resonance imaging (MRI) is an excellent tool for early diagnosis as well as for follow-up of response to treatment in affected AAJ in patients with rheumatoid arthritis. It has the ability to detect synovitis (synovial enhancement), periarticular bone marrow edema (BME), enhanced pannus formation, joint effusion, and erosion (5).

Systemic steroids have been conventionally used to treat inflammation of the AAJ (6). Regrettably, these have many unwanted side effects. Intraarticular glucocorticoid injection is considered a treatment option for AAJ arthritis without the side effects of systemic steroids (7-9). The aim of this study is to evaluate clinically and radiologically the effectiveness of intraarticular glucocorticoid injection of the AAJ affected by rheumatoid arthritis.

Methods

The current study was approved by the ethical committee of the faculty of medicine at Assuit University after obtaining written and informed consent from each participant. The trial was registered in Australian New Zealand Clinical Trials Registry, trial ID: ACTRN12616000750482.

Inclusion criteria comprised patients with rheumatoid arthritis suffering from upper neck pain and or headache due to inflamed AAJ rated on 100-point visual analog scale (VAS) ≥ 50, should have MRI evidence of acute inflammation of AAJ (BME, synovial enhancement, and or pannus), and C reactive protein of ≥ 12.

Exclusion criteria included neck pain because of other pathology such as disc herniation or cervical spondylosis, pregnancy, untreated coagulopathy, and allergy to iodinated dye.

The included patients were randomized according to a computer generated list of numbers into 2 groups. Group AAJI (n = 30) received AAJ injection with 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of 20 mg of triamcinolone, in addition to oral placebo tablets (2 tablets every 8 hours for one week). Group SS (n = 30) received systemic steroids, oral prednisolone tablets (5 mg, 2 tablets every 8 hours for one week), in addition to AAJ injection with 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of normal saline solution.

AAJ Injection Procedure

The patient was placed in the prone position and a pillow placed under the chest to allow for slight neck flexion, the upper neck was sterilized and draped, the C-arm was brought to the head of the patient, and an anteroposterior image was obtained. Then the C-arm was rotated in a cephalad-caudad direction to obtain the best view for the lateral AAJ. The needle insertion site was marked on the skin overlying the junction of the middle and lateral thirds of the AAJ. A skin wheel was raised with 2 mL of xylocaine 1% at the insertion site. Then a 22G 3.5 inch blunt needle was advanced toward the posterolateral aspect of the inferior margin of the inferior articular process of the atlas (C1). Then a lateral view was obtained. The needle was withdrawn slightly, directed toward the joint line of the AAJ, and advanced only 2 mm. Usually, a distinctive pop is felt indicating entry to the joint cavity. After careful negative aspiration for blood or cerebrospinal fluid, 0.2 mL of Omnipaque (GE Healthcare Inc., Ireland, Cork, Ireland) dye was injected to verify intraarticular placement of the tip of the needle under direct real-time fluoroscopy to check for inadvertent intraarterial injection. Anteroposterior and lateral views were obtained to ensure that the contrast medium remained confined to the joint cavity without escape to the surrounding structures, and finally, 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of 20 mg of triamcinolone or 1.0 mL of a mixture of 0.5 mL of bupivacaine 0.5% and 0.5 mL of normal saline solution was injected according to group allocation (10). The same procedure was repeated for the other side (Fig. 1).

Medications Received by Both Groups

Intramuscular methotrexate 12.5 mg per week and hydroxychloroquine (oral tablet 200 mg) 2 tablets per day (regular treatment for patients with rheumatoid arthritis that continues for life), and short course treatment (5 days) of nonsteroidal anti-inflammatory drugs (celecoxib, 200 mg) once daily was allowed when the intensity of neck pain exceeded 5 on VAS pain score.

Follow-Up

The 2 groups were followed up with the neck disability index (NDI), VAS pain score, and MRI (11).

NDI and VAS pain scores were evaluated by a rheumatologist every 2 weeks for a 3 month follow-up period, and MRI was requested 4 weeks postoperatively and comparison of radiologic changes for each patient pre- and post-AAJ injection was evaluated by a radiologist. Both the rheumatologist and the radiologist concerned with data collection were blinded to the type of intervention that was received by each patient.

MRI of the cervical spine was performed using a 1.5 Tesla scanner (Achieva, Philips, the Netherlands). The patients were positioned supine with a neck coil around the neck in a neutral position. Special emphasis was made on the sequences of sagittal T2-weighted fast spin-echo (repetition time (TR)/echo time (TE): 2880-3000/120 msec, slice thickness/slice gap: 3/0.3 mm) and short tau inversion recovery (STIR) images (TR/TE: 2800-3200/70-120 msec, slice thickness/slice gap: 4/0.6 mm), as well as pre- and postcontrast medium injection images of sagittal and axial T1-weighted fast spin-echo (TR/TE: 400-430/8 msec, slice thickness/slice gap: 3/0.3 mm), postcontrast images were obtained 5 minutes after injection. The sagittal images were obtained with a field of view of 160 x 251 x 50 mm and reconstruction matrix of 512 x 512. The axial images were obtained with a field of view of 170 x 170 x 66 mm and reconstruction matrix of 352 x 352.

The primary endpoint was the percentage of patients who showed ≥ 50% reduction of their VAS pain score. The secondary endpoints were VAS and NDI measured at 2, 4, 6, 8, and 12 weeks postoperatively, and the MRI changes of AAJ assessed 4 weeks postoperatively.

Statistical Analysis

Statistical analysis was performed on a personal computer using SPSS version 20 software (IBM, Armonk, NY). The data were checked for normality using the Anderson–Darling test prior to statistical analysis. The VAS pain score and the NDI were normally distributed using the Anderson–Darling test. We assessed the effects of group, time, and the group-by-time interaction on mean VAS pain score and NDI over time (2, 4, 6, 8, and 12 weeks postoperatively) using the general linear model. Qualitative data were reported as counts and percentages, and differences between groups were analyzed with the chi-square test or the Fisher exact test, as appropriate, in which continuous data were described as mean ± standard deviation (SD) and 95% confidence interval (CI); differences between groups were analyzed with the t test. The type I error was controlled with the Bonferroni correction when conducting the multiple tests. $P < 0.05$ was considered statistically significant.

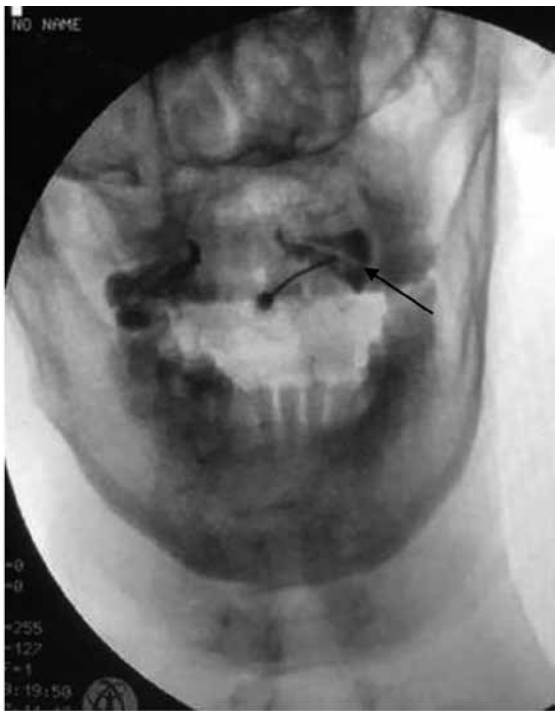

Fig. 1. *X-ray image, open mouth view showing the lateral AAJ delineated by the dye and the needle inside the joint cavity. The arrow is pointing to the AAJ line.*

Based on a previous study (12), claimed that a 25% of patients showed ≥ 50% reduction of their pain that lasted for 3 months following AAJ steroid injection. We assume that AAJ steroid injection would achieve ≥ 50% reduction of pain in 50% of patients. Therefore, the required sample size would be 55 patients, considering the confidence level is set at 95% with 80% power and 5% alpha error. To allow for possibility of dropouts, we enrolled 60 patients.

Results

A total of 75 patients were assessed for eligibility; 15 patients did not fulfill the inclusion criteria, and 2 patients in group SS were lost to follow-up. In group AAJI, one patient did not receive injection owing to failure of visualization of the AAJ line, and another patient was lost to follow-up; 28 patients in each group remained for statistical analysis (Fig. 2).

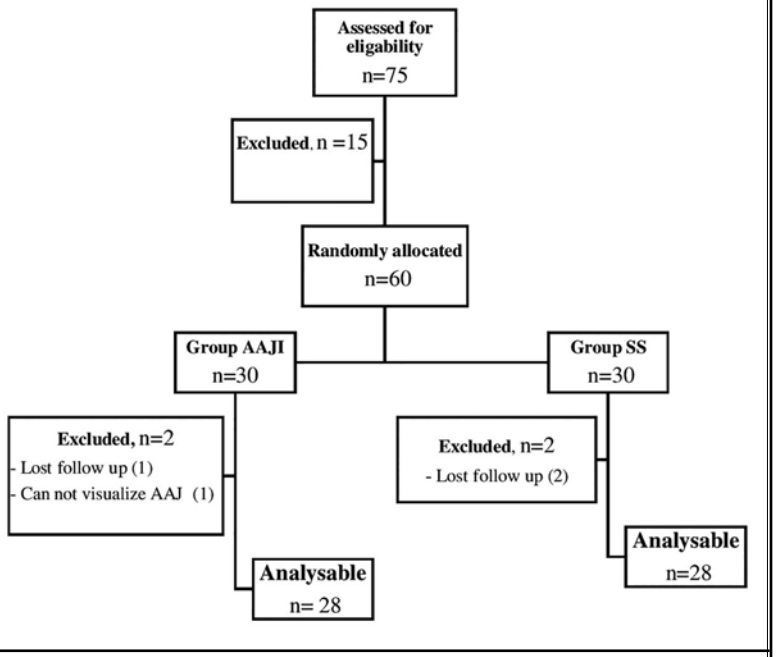

Fig. 2. *Flow chart of the patients through the study.*

Table 1. *Demographic data and postoperative radiologic changes of AAJ detected by MRI.*

Variable		Group AAJI n = 28	Group SS n = 28	P Value
Age		40 ± 8	42 ± 10	0.987
Gender (female:male)		26:2	25:3	0.988
BMI		27 ± 6	25 ± 5	0.862
BME (disappeared)		20/28, 71.4%	12/28, 42.9%	0.035
Synovial enhancement (disappeared)		16/22, 72.7%	10/23, 43.5%	0.026
Pannus	no change	3/10, 30%	6/9, 66.67%	0.128
	decreased	6/10, 60%	1/9, 11%	0.041
	increased	1/10, 10%	2/9, 22%	0.482

Data presented as means ± SD, numbers and percentages. P < 0.05 is considered statistically significant. BMI, body mass index

The 2 groups were similar regarding demographic data and patient characteristics (Table 1).

There was significant reduction of the percentage of patients who showed > 50% reduction of their VAS pain score postoperatively in group AAJI compared with group SS at one month (75% vs. 46.45; *P* = 0.033), 2 months (60.7 vs. 25; *P* = 0.009), and 3 months (53.6 vs. 17.9; *P* = 0.007) (Table 2).

Analysis of postoperative pain over time (2, 4, 6, 8, and 12 weeks) using the general linear model revealed significant reduction of overall VAS in group AAJI compared with group SS (mean ± SE) (41.5 ± 2.6 vs. 52.1 ± 2.6; *P* = 0.005), with significant group, time, and group-by-time interaction effect. Further point-by-point comparison of VAS revealed significant reduction in group AAJI compared with group SS at all time points (2, 4, 6, 8, and 12 weeks) (mean ± SD, 95% CI of mean difference) at 2 weeks, (37 ± 16 vs. 52 ± 12, [–15 (–23: –8)]; *P* = 0.000), at 4 weeks (32 ± 18 vs. 43 ± 13, [–11 (–19: –2)]; *P* = 0.013), at 6 weeks (35 ± 19 vs. 51 ± 18, [–15 (–25: –6)]; *P* = 0.002), at 8 weeks (38 ± 19 vs. 53 ± 20, [–15 (–25: –5)]; *P* = 0.003), and at 12 weeks (39 ± 15 vs. 53 ± 19, [–14 (–23: –5)]; *P* = 0.004) (Table 3).

Analysis of postoperative NDI over time (2, 4, 6, 8, and 12 weeks) using the general linear model revealed significant reduction of overall NDI in group AAJI compared with group SS (mean ± SE) (43.7 ± 3.1 vs. 52.4 ± 3.1; *P* = 0.040) with significant group, time, and group-by-time interaction effect. Further point-by-point comparison of NDI revealed significant reduction in group AAJI compared with group SS at the following time points, at 4 weeks (40.14 ± 19 vs. 49.29 ± 12, [–9 (–18: –0.7)]; *P* = 0.035), at 6 weeks (33.43 ± 18 vs. 48.71 ± 19, [–15 (–25: –5)]; *P* = 0.003), at 8 weeks (37.68 ± 19 vs. 52.14 ± 19, [–14 (–25: –4)]; *P* = 0.006) and at 12 weeks (41.75 ± 21 vs. 52.96 ± 20, [–11 (–22: –0.3)]; *P* = 0.045), however, there was no significant reduction at 2 weeks postoperatively (42.21 ± 18 vs. 48.86 ± 15, [–7 (–16:2)]; *P* = 0.142) (Table 3).

Analysis of postoperative MRI findings revealed significant improvement of BME in group AAJI (AAJI vs. SS) (71.4% vs. 42.9%; *P* = 0.033), also the synovial enhancement disappeared significantly in group AAJI

compared with group SS (16/22 [72.7%] vs. 10/23 [43.5%]; $P = 0.026$), moreover, there was a significant reduction in pannus size in group AAJI compared with group SS (6/10 [60%] vs. 1/9 [11%]; $P = 0.041$) (Table 1, Fig. 3).

Regarding the side effects reported during the study period, in group AAJI 17 patients complained of pain during injection and one patient complained of dizziness that recovered spontaneously within 10 minutes. In the group SS, one patient suffered from hypertension, 2 patients suffered from hyperglycemia, and 4 patients complained of gastric upset. All these side effects were controlled, and the patients completed the steroid course.

Table 2. *Patients showed ≥ 50% reduction in their initial VAS pain score.*

Variable	Group AAJI n = 28	Group SS n = 28	*P* Value
At 1 month	21/28, 75%	13/28, 46.4%	0.033
At 2 months	17/28, 60.7%	7/28, 25%	0.009
At 3 months	15/28, 53.6%	5/28, 17.9%	0.007

Data presented as numbers and percentages. P < 0.05 is considered statistically significant.

Table 3. *Postoperative VAS pain score and NDI score.*

Variable	Group AAJI n = 28 Mean ± SD	Group SS n = 28 Mean ± SD	Mean Difference (95% CI)	*P* Value
VAS, preoperative	67 + 11	63 + 13	4 (–2: 10)	0.197
VAS, 2 wks	37 ± 16	52 ± 12	–15 (–23: –8)	0.000
VAS, 4 wks	32 ± 18	43 ± 13	–11 (–19: –2)	0.013
VAS, 6 wks	35 ± 19	51 ± 18	–15 (–25: –6)	0.002
VAS, 8 wks	38 ± 19	53 ± 20	–15 (–25: –5)	0.003
VAS, 12 wks	39 ± 15	53 ± 19	–14 (–23: –5)	0.004
NDI, preoperative	64.39 ± 21	62.39 ± 19	2 (–9: 13)	0.708
NDI, 2 wks	42.21 ± 18	48.86 ± 15	–7 (–16: 2)	0.142
NDI, 4 wks	40.14 ± 19	49.29 ± 12	–9 (–18: –0.7)	0.035
NDI, 6 wks	33.43 ± 18	48.71 ± 19	–15 (–25: –5)	0.003
NDI, 8 wks	37.68 ± 19	52.14 ± 19	–14 (–25: –4)	0.006
NDI, 12 wks	41.75 ± 21	52.96 ± 20	–11 (–22: –0.3)	0.045

Data presented as means ± SD and mean difference (95% CI). P < 0.05 is considered statistically significant.

Discussion

Intraarticular steroid injection of the AAJ affected by rheumatoid arthritis reduced neck pain, improved neck mobility, and hastened resolution of acute AAJ arthritis.

To the best of our knowledge, this is the first prospective intervention controlled study to evaluate the efficacy of intraarticular steroid injection of rheumatoid-affected AAJ, clinically in the form of measurements of neck pain severity and disability, as well as radiologically in the form of postinjection MRI changes of the AAJ.

Overall, the intensity of neck pain and disability were decreased over time in group AAJI in comparison to group SS, however, the percentage of patients in group AAJI that showed > 50% reduction of their initial pain was decreased over time from 75% at one month following injection to 53.6% at 3 months following injection.

The reduction over time of the percentage of patients that showed ≥ 50% reduction of their initial pain is indicative of 1; the best benefit is obtained when the AAJ is injected with steroids during acute inflammatory stage, 2; the relatively short time advantage of AAJ injection and 3; the necessity for repeated joint injection to obtain a good results.

In this context, Narouze et al (12) stated that AAJ intraarticular steroid injection for patients with cervicogenic headache, whose clinical picture is suggestive of AAJ pain, decreased VAS pain score from a baseline of 6.8 to 1.9 at one month, 3.6 at 3 months, and 3.7 at 6 months postinjection, and they concluded that intraarticular steroid injection is effective in short-term relief of pain originating from the lateral AAJ.

Narouze et al (12) did not determine the nature of pathology of AAJ in included patients. In contrast, we enrolled only patients who had MRI findings suggestive of acute inflammation of AAJ, and we did not solely rely on indicative clinical findings "occipital and suboccipital pain and tenderness" because these clinical signs have a positive predictive value of only 60% (13).

In agreement with our findings, Glémarec et al (14) detected a better analgesic response rate for patients with inflammatory AAJ disorder than a mechanical one (response rate 100% vs. 50%; pain scale score decrease 80 ± 27% vs. 34.2 ± 40%).

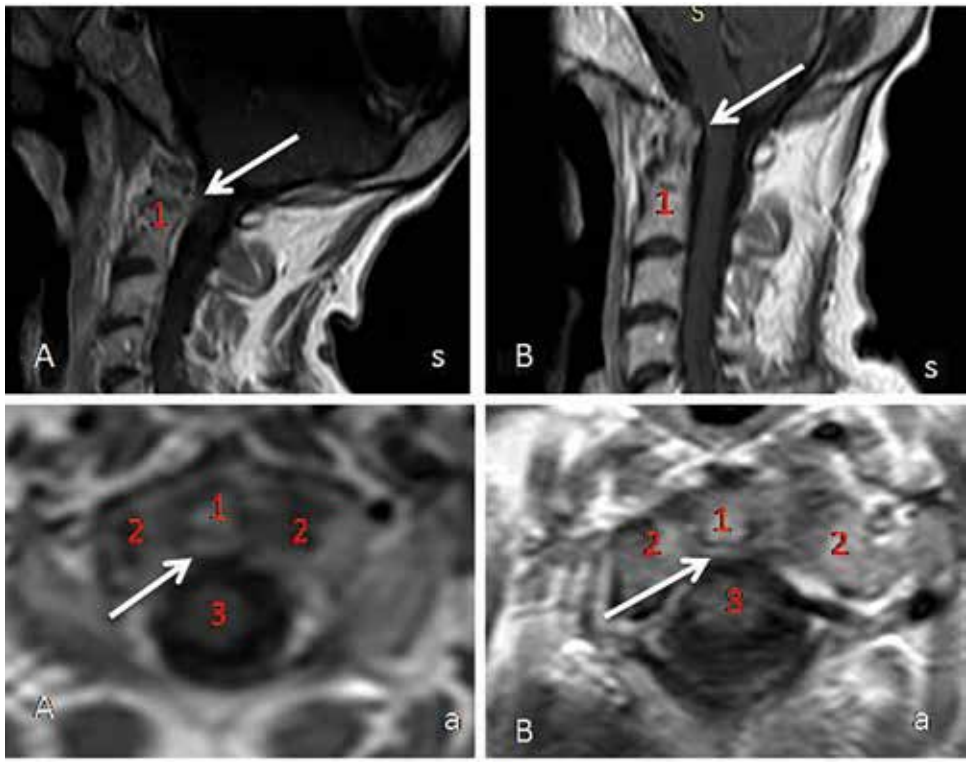

Fig. 3. *(A) Pre and (B) postinjection sagittal (s) and axial (a) postcontrast T1-weighted images of the AAJ of a 60-year-old patient with rheumatoid arthritis showing the marked reduction in enhanced pannus size (white arrows) seen posterior to the odontoid process. 1) odontoid process; 2) lateral C1 masses; and 3) spinal cord.*

Intraarticular corticosteroid injection is a well-established adjunctive treatment for the management of rheumatoid arthritis (15), that lacks the hazards of long-term steroid use specifically, "osteoporosis, increased susceptibility to infection, hypertension, diabetes mellitus, as well as many other side effects" (16). In general, intraarticular injection of corticosteroids has been shown to provide clinical benefit up to 6 months and even longer (15). From a pharmacological standpoint, corticosteroid injection is able to decrease the expression of citrullinated proteins, monoclonal antibody F95, and peptidylarginine deiminase in rheumatoid arthritis synovium (17), and thus, it suppresses rheumatoid-induced synovitis that is largely responsible for the disease-associated joint destruction and subsequent disability (18).

In contrast to systemic steroids, the side effects of intraarticular steroids are low (19). A postinjection flare occurs as a result of crystal-induced synovitis in about 1%-2% of patients. Surprisingly, septic arthritis following intraarticular injection is very rare (0.005%). The crystalline suspensions (e.g., triamcinolone) used in the current study have the advantage over soluble preparations (e.g., dexamethasone) of providing prolonged relief. However, a postinjection flare, as previously mentioned, is possible (16). In the current study, AAJ injection has significantly reduced the periarticular BME, synovial enhancement, and pannus size (Figs. 3). MRI reveals proliferative synovitis as thickening of the synovial membrane, which has intermediate to low signal intensity on T1-weighted images and, owing to increased water content of synovitis, high signal intensity on T2-weighted and STIR images. Contrast-enhanced T1-weighted images are more sensitive and specific in the assessment of acute synovitis than noncontrast MRI. On postcontrast images, the inflamed synovium shows fast enhancement, which lasts approximately 5 minutes after injection. BME is seen as hyperintense T2 signal area within trabecular bone with ill-defined margins and signal characteristics consistent with increased water content, that is, high signal on T2 fat suppression (FS) and STIR images, and increased signal intensity after the administration of gadolinium-based contrast medium. With T1-weighted sequences, BME has low signal intensity, but changes are less conspicuous compared with other pulse sequences (20).

It is fundamental to pain interventionist to be familiar with the anatomy of the AAJ to avoid injury of the nearby vertebral artery and neural structures (C2 nerve root and spinal cord) (21). The vertebral artery is just lateral to the AAJ as it courses through the C2 and C1 foramina, then curves medially crossing the medial posterior aspect of the atlanto-occipital joint to go through the foramen magnum. The C2 nerve root, dorsal root ganglion, and its surrounding dural sleeve cross the posterior aspect of the middle of the AAJ. Therefore, during AAJ injection, the needle should be directed toward the junction of the middle and lateral thirds of the posterior aspect of the joint. This will avoid injury to the C2 nerve root medially or the vertebral artery laterally. Complications are generally rare, and we did not detect any complication related to AAJ injection in the current study apart from pain during injection; however, too lateral a placement of the needle can injure or inject through the vertebral artery that results in devastating neurologic complications, and too medial a placement may inject through the dural sleeve of C2 resulting in high spinal block.

Ultimately, the rheumatologist and pain interventionist should weight the risk of AAJ destruction and subsequent neurologic damage and the complications related to injections, which are very rare when the technique is done by experienced pain interventionist under real-time fluoroscopy and possibly ultrasound guidance.

Study Limitations

First, the authors did not perform a diagnostic AAJ injection to confirm that the lateral AAJ is the source of upper neck pain; instead we depended on MRI findings suggestive of acute inflammation of the AAJ. Second, the authors did not request serial MRI for radiologic follow-up postprocedure and they requested it only once at 4 weeks postprocedure. Third, the postinjection follow-up period is limited to only 3 months, which is relatively a short duration. Therefore, future studies are needed to overcome these limitations.

Conclusions

For acutely inflamed AAJ due to rheumatoid arthritis, AAJ steroid injection is a potential therapeutic option; it decreased cervical neck pain, improved neck mobility, and hastened recovery of the joint from an acute inflammatory stage.

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